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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/560,734 | 12/15/2005 | Timo Heinrich | MERCK-3099 | 3735 |

23599 7590 05/21/2009

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| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 05/21/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/560,734 | HEINRICH ET AL. | |
| | Examiner | Art Unit | |
| | NOBLE JARRELL | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,6-9,12,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,8,9,12,14 and 15* is/are rejected.

7)☒ Claim(s) *1-3,6 and 7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/25/2009 has been entered.

2. In the current set of claims, claims 1-4, 6-9, 12, 14, and 15 are pending.

### *Claim Objections*

3. Claims 1, 2, 4, 6-9, 12, and 14-15 are objected to because of the following informalities: the exact meaning of the dashed line in compounds of formula I needs to be defined (without the introduction of new matter). Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 8 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants do not give any guidance for the required additional "medicament active ingredient" required in these claims. The only way to possibly define the ingredient is through a property, and this property is that it is medically active. This property fails to clearly define what exact compounds applicants intend to put together with compounds f formula I. Based on the state of the art, applicants could mean repinostan (discussed

under 112 1st scope of enablement rejection). However, the examiner is not sure because the only guidance is that the compound is medically active.

6. Claims 8, 9, 14, and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for simple composition (a composition with a compound, one or more inert pharmaceutically acceptable carrier(s) and no other pharmaceutically active compounds) comprising a compound of formula I and salts and stereoisomers of compounds of formula I, does not reasonably provide enablement for complex compositions (a composition comprising a compound, one or more inert pharmaceutically active carrier(s), and at least one additional pharmaceutically active compound) comprising a compound of formula I or for solvates of compounds of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

*(1) The nature of the invention and (2) the breadth of the claims*:

The claims are drawn to compounds in which an indoline ring is connected to a piperazine or piperidine ring through a $C_mH_{2m}$ (where m is an integer from two to six) linker. The piperazine or piperidine ring is modified with a $C_nH_{2n}$-benzofuran (where n is an integer from zero to four) group. Claims are also drawn to compositions comprising compounds with this core structure. Thus, the claims taken together with

the specification imply that complex composition and/or solvates of formula I can be prepared.

*(3) The state of the prior art and (4) the predictability or unpredictability of the art:*

Vippagunta et al. (*Advanced Drug Delivery Reviews*, **2001**, *48*, 3-26, cited previously) teach that solvate or hydrate formation is unpredictable among a series of related compounds because each compound responds uniquely to solvate or hydrate formation (page 18, section 3.4).

*(5) The relative skill of those in the art:*

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of solvates of compounds of formula I and complex compositions comprising compounds of formula I.

*(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:*

The specification has provided guidance for preparation of salts or stereoisomers of compounds of formula I.

However, the specification does not provide guidance for complex compositions of formula I and solvates of compounds of formula I. Applicants only show the preparation of simple compositions comprising compounds of formula I (examples 6-13, pages 24-25). No guidance is given as to the ratio of active compounds in a complex composition or even the intended additional active agent.

*(8) The quantity of experimentation necessary:*

Considering the state of the art as discussed by the references above, particularly with regards to claims 8, 9, 14, and 15 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

7. Claims 12 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *in vitro* binding of 5-$HT_{1A}$ and SSRI (selective serotonin reuptake inhibitors) compounds (specifically 5-{4-[4-(5-cyano-2-oxo-2,3-dihydro-1H-indol-3-yl)butyl)butyl]piperazine-1-yl}benzofuran-2-carboxamide), does not reasonably provide enablement for treatment of migraine headaches, cerebral infarctions, and obsessive-compulsive disorder (OCD), nor for the simultaneous treatment and prevention of each of these disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

*(1) The nature of the invention and (2) the breadth of the claims*:

The claims are drawn to a method of treating and/or preventing migraine headaches, cerebral infarctions, or obsessive-compulsive disorder with compounds in which an indoline ring is connected to a piperazine or piperidine ring through a $C_mH_{2m}$ (where m

is an integer from two to six) linker. The piperazine or piperidine ring is modified with a $C_nH_{2n}$-benzofuran (where n is an integer from zero to four) group.. Thus, the claims taken together with the specification imply that treatment and/or prevention of migraine headaches, cerebral infarctions, or obsessive-compulsive disorders.

*(3) The state of the prior art and (4) the predictability or unpredictability of the art:*

Pillay et al. (*Expert Opinion on Investigational Drugs*, **2007**, *12(4)*, 541-54) teach that 5-$HT_{1A}$ is a possible therapeutic target for anxiety disorders (page 544-45, section 5.1). Obsessive-compulsive disorder is one example of an anxiety disorder (page 541, sec 1, first paragraph). This reference teaches that future research is required to determine if 5-$HT_{1A}$ is a viable *in vivo* target for the treatment of OCD.

Legos et al. (*Expert Opinion on Investigational Drugs*, **2002**, *11(5)*, 603-614) teach that repinostan is currently undergoing clinical trials for treatment of ischaemia (page 609, section 5.2). In repinostan, a benzothiazole is connected to a NH-CH(benzopyran) group through a butylene chain. Hence, the only similarity between repinostan and compounds of formula I is a butylene chain. In compounds of formula I, an indoline ring is connected to a piperazine or piperidine ring through an alkaline linker containing two to six carbons (and the piperazine or piperidine ring is further modified with an alkylene-benzofuran moiety). Beside the butylene chain, none of the other groups in this comparison are similar. Hence, applicants are not enabled for ischaemia based on these dissimilarities.

Waeber (*Expert Opinion on Investigational Drugs*, **2003**, *8(2)*, 437-56) teaches that migraines are treated through the 5-$HT_{2A}$ receptor possibly. This reference teaches that migraine headaches are controlled through the 5-$HT_{2A}$ receptor (not 5-$HT_{1A}$ or

SSRI's) and that future research is required to definitely prove that the 5-$HT_{2A}$ receptor is a viable *in vivo* target for treatment of migraine headaches.

*(5) The relative skill of those in the art:*

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in the treatment and/or prevention of migraine headaches, cerebral infarctions, and obsessive-compulsive disorder.

*(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:*

The specification has provided guidance for *in vitro* binding of compounds of formula I to 5-$HT_{1A}$ or SSRI's.

However, the specification does not provide guidance for treatment, prevention, or simultaneous treatment and prevention of any disease or disorder controlled by a 5-$HT_{1A}$ receptor or an SSRI.

*(8) The quantity of experimentation necessary:*

Considering the state of the art as discussed by the references above, particularly with regards to claims 12 and 15 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 4, 8, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the conversion to a compound of formula I in processes B and C. Only process A shows how the saturated indole ring is converted to an indoline ring (the 2,3-dihydro form of indole). Regarding claims 8 and 14, what is the additional active ingredient in the composition or kit? Applicants do not provide any guidance as to the intended agent. Examples 6-13 (pages 24-25) fail to clarify this claim as well because each of the compositions or kits formed only consists of a compound of formula I and an inert carrier.

***Conclusion***

10. Claim 3 is objected to as being dependent upon a objected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. Claim 3 appears free of the prior art because compound a) of claim 6 of Dorsch et al. (WO 02/083666, published 24 October 2002, cited in IDS) contains an indole ring instead of indoline ring (2, 3-dihydro-indole ring). Thus compounds of claim 3 because a double bond is not considered anticipatory or obvious over a single bond.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

For James Wilson,
/Kahsay T. Habte/
Primary Examiner, Art Unit 1624